

New autoantibodies and their clinical associations in juvenile myositis – a systematic review

Daniela Peixoto¹, José Costa¹, Marta Ferretti², Clara Malattia^{2,3}, Alberto Martini^{2,3}

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ABSTRACT

Background: Novel autoantibodies targeting intracellular proteins are recently detected in patients with idiopathic inflammatory myopathies (IIMs).

Objective. To evaluate the prevalence of these myositis-specific antibodies (MSAs) in juvenile IIMs (JIIMs) and their association with clinical characteristics and disease course.

Methods: A systematic literature search was carried out to identify all studies concerning these novel MSAs (p155/140, p140, CADM-140, SAE and 200/100) in patients with JIIMs. Results: A total of 1003 references were identified, of which 118 were selected for detailed analysis and 13 included in the final review.

Conclusions: The anti-p155/140, the anti-p140 and the anti-CADM-140 seem to be useful markers for define distinct clinical subsets and for predicting prognosis of JIIMs. Further studies are needed to clarify the importance of anti 200/100 and anti-SAE in juvenile myositis.

Keywords: Myositis-specific antibodies; Novel autoantibodies; Juvenil idiopathic inflammatory myopathies.

INTRODUCTION

Juvenile idiopathic inflammatory myopathies (JIIMs) include a heterogeneous group of rare disorders of unknown aetiology characterized by chronic inflammation of skeletal muscle and result in significant morbidity and mortality^{1,2}. Juvenile dermatomyositis represents the most common IIM in childhood. The in-

cidence varies depending on the population and ethnicity and is approximately 1.9 to 4.1 per million children per year³.

Although the aetiology of JIIMs remains unclear, it has been suggested that environmental triggers, immune dysfunction and specific tissue responses in genetically susceptible individuals, play a crucial role in disease onset⁴.

As other autoimmune diseases, autoantibodies can be found in the sera of these patients. Autoantibodies can be divided into two categories: myositis-specific antibodies (MSAs) and myositis-associated antibodies (MAAs). The MSAs (anti-Jo-1 and the less common non-Jo-1 anti-synthetases, anti-SRP and anti-Mi-2) are relatively specific for myositis while the MAAs (anti-PMScl, anti-Ku, anti-U1RNP, and anti-U3RNP) are also found in other autoimmune conditions and overlap syndromes¹.

The “traditional” MSAs (anti-Jo-1, anti-Mi2 and anti-SRP) can be detected by routine commercial assays but have been identified in a small percentage of JIIMs patients. Anti-Mi2 is the “classical” DM autoantibody discovered in 20% of adult myositis and 4 to 10% of those with JDM4. It is associated with hallmark cutaneous features and milder muscle disease. It carries a good prognosis both in adults and children^{5,6}. Anti-SRP antibody, present in 5% of adult IIMs, is associated with necrotizing myopathy and profound muscle weakness. This autoantibody has rarely been identified in JIIMs⁶.

Anti-Jo1 are found in 40% of adult patients and are associated with a distinct clinical phenotype known as the anti-synthetase syndrome, comprising myositis, interstitial lung disease (ILD), arthritis, fever, Raynaud’s phenomenon and mechanic’s hands⁶. These autoantibodies are rare in JDM, however affected children may have clinical features similar to anti-synthetase syndrome in adults^{5,6}.

Over the last few years, novel MSAs have been identified, including anti-p155/140, anti-p140, anti-SAE,

1. Department of Rheumatology, ULSAM – Conde de Bertiandos Hospital, Ponte de Lima, Portugal

2. Department of Rheumatology, Pediatria II – Istituto Giannina Gaslini, Genoa, Italy

3. Department of Pediatrics, University of Genoa, Italy

anti-CADM-140 and anti-200/100.

Several studies in adult's myositis have widely demonstrated the association between these autoantibodies and clinical subsets within the IIM spectrum, as well as their potential value in predicting clinical outcomes, (i.e. the association with malignancy or with development of severe cutaneous disease). In contrast to the many studies performed in adults, to our knowledge, very few studies have explored the frequency and the clinical associations of these autoantibodies in juvenile myopathies.

This review highlights the potential value of these new autoantibodies in JIIM and their association with clinical characteristics and disease course.

METHODS

A systematic review of the published literature following the methods of evidence based medicine was performed.

TYPE OF PARTICIPANTS

The analysis was restricted to patients with the diagnosis of JIIMs.

TYPES OF STUDIES

We considered all observational studies which assessed the frequency of these novel autoantibodies in JIIMs namely the anti-p155/140, anti-p140, anti-SAE, anti-CADM-140 and anti-200/100 and their relationship with clinical characteristics and disease course. We excluded articles that clearly did not address the topic of interest and all case reports.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

ELECTRONIC SEARCHES

We used the following computerized bibliographic databases to identify relevant studies: the Cochrane Central Register of Controlled Trials (CENTRAL) of The Cochrane Library, MEDLINE and EMBASE. The search was restricted to English, French, Portuguese, Spanish or Italian language articles published up to May 2013. We used specific MeSH headings and additional keywords to identify all relevant studies.

SEARCHING OTHER RESOURCES

We manually searched the bibliographies of all inclu-

ded papers for information on any other relevant studies. We also reviewed the annual scientific conference abstracts for the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) from 2011 to 2012, to identify unpublished studies.

RESULTS

Initially, the search of databases as registered above resulted in 1003 papers, of which 118 were selected for detailed analysis and 13 included in the final review.

ANTI-P155/140

The anti-p155/140 antibodies were described the first time by Targoff and colleagues (2006), in adults and children's with IIMs⁷. This antibody is thus designated based on the molecular weights of the polypeptide targets (155 and 140 kDa). In 2007, the 155-kDa autoantigen target was identified as transcription intermediary factor 1 gamma (TIF1)⁸. TIF1 is a nuclear factor that, via SMADA4, plays an important role in transforming growth factor- β signaling and suppression of cell growth⁵. The identification of the 140kDa autoantigen has yet to be established, although it seems to be a degradation product of TIF1- or possibly TIF1, an isoform that has a molecular weight of 140 kDa^{5,9}. Anti-p155 is found usually in association with anti-TIF1 (anti-p155/140) and occasionally anti-TIF1 β ⁹.

Targoff *et al.* screened 127 JIIMs by radiolabeled immunoprecipitation (IPP) and found that 28% of JIIMs were positive for this autoantibody⁷. Subsequently, others authors have detected anti-p155/140 autoantibodies in 22%-36% of the patients with JIIMs (Table I)⁸⁻¹¹. In all these studies, this antibody was more frequent in JDM and none of the patients with juvenile polymyositis (JPM) showed positivity to anti-p155/140. However, this antibody was not specific for JDM, since it was found in patients with myositis in the context of other connective tissue diseases.

In adults, this antibody was detected in 13% to 21% of DM, and was strongly associated with the development of malignancy⁶. Although the anti-p155/140 autoantibody has been demonstrated to target the same autoantigens in adults and children s with DM, there are some clinical differences. In particular, the significant association with malignancy in adults, was not observed in anti-155/140-positive JDM cases⁷⁻¹⁰. Furthermore, also young adults positive for this autoanti-

TABLE I. SUMMARY OF THE STUDIES CARRIED ON THE ANTI-P155/140 IN JIIMS

Author, year	Study/Population studied	Antibody frequency in JIIMS	Clinical associations
Targoff (2006)	<u>Controlled study</u> 244 IIMs (J+A) - 127 JIIMs 138 controls: healthy subjects, others	JIIMs: 28% (n=35) - 30 JDM, 5 JCDT-M, 0 JPM Controls: 0.7%	<u>JIIMs: NR</u> <u>Adults anti p155/140+</u> versus antisynthetase+: - Higher frequency of V-sign rash (p<0.05.) myopathies and CTD - Malignancy was present in 37.5%
Gunawardena (2008)	<u>Controlled study</u> 116 JDM 285 controls: healthy subjects, ADM and others CTD	JIIMs: 23% (n=27) - 26 JDM, 1 JCDT-M Controls: 6 ADM (n=30%), 0 others	<u>JDM anti p155/140+ versus anti p155/140-:</u> - Higher frequency of Gottron's papules (p<0.05) and skin ulceration (p<0.05)
Espada (2009)	<u>Uncontrolled study</u> 64 JIIMs	JIIMs: 22% - 11 JDM, 3 JCDT-M	<u>Anti p155/140 + versus MAAs and anti-p140-</u> - More cutaneous vasculitis and arthritis (p value NR)
Fugimoto (2012)	<u>Controlled study</u> 456 DM (J+A) - 11 JDM 603 controls: PM and others CTD	JDM: 36% (n= 4) ADM: 17% (n=74) vs. Controls: 0.33% (n=2)	<u>JDM: No cancer association</u> <u>Adults with DM anti p155/140+:</u> - 65% (n=48) had cancer
Shah (2013)	<u>Uncontrolled study</u> 436 JIIMs	JIIM: 30% (n=131) - 123 JDM, 0 JPM, 8 JCDT-M	Anti p155/140 was more frequent in JDM than in JPM and JCTM (p<0.05)

IIMs: idiopathic inflammatory myopathies; A: adults; J: juvenile; JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; JCDT-M: juvenile connective tissue disease associated myositis; CDT: connective tissue disease; MAAs: myositis-associated antibodies

body do not appear predisposed to malignancy⁹.

As for adults, however, children anti-p155/140-positive appears to have more severe cutaneous involvement. Gunawardena *et al.* reported that JDM patients anti-p155/140-positive had significantly more Gottron's papules, ulceration and oedema than anti-p155/140-negative cases¹⁰. Furthermore, Espada *et al.* found that the children anti-155/140 positive also had cutaneous vasculitis and suffered more arthritis¹¹ (Table I).

ANTI-P140 OR ANTI-MJ (NPX2)

The anti-p140, originally termed anti-MJ, was found in 12-25% juvenile DM¹¹⁻¹⁴. Evidence suggests that MJ autoantigen might be a nuclear matrix protein (NXP-2 or MORC3) involved in nuclear transcription, essential for regulating the activation of tumor sup-

pressor gene p536,14.

Anti-p140 is uncommon in adults (1.6% of patients) and disease associations have yet to be firmly established⁶. Conversely, it seems to be more frequent in JIIMs, being described in 12-25% of the affected children (Table II).

Espada *et al.* evaluated the presence of this antibody in 64 JIIMs, and found an association between this antibody and muscle contractures, atrophy, a worse functional status and more persistent activity⁸. In two controlled studies with a large number of JIIMs, Gunawardena and Tansley found that anti-p140 antibodies are significantly associated with an increased frequency of calcinosis^{13,14}.

ANTI-CADM 140 (MDA5)

Autoantibodies against 140-kDa cytoplasmic protein

TABLE II. SUMMARY OF THE STUDIES CARRIED ON THE ANTI-P140 IN JIIMS

Author, year	Study/Population studied	Antibody frequency in JIIMs	Clinical associations
Gunawardena (2009)	<i>Controlled study</i> 162 JIIM 123 controls: others CTD	JIIMs: 23% (n=37) - all DM 0 other conditions	<u>Anti-p140+ versus anti-p140-:</u> - higher incidence of calcinosis, (p <0.05)
Espada (2009)	<i>Uncontrolled study</i> 64 JIIMs	JIIMs: 25% (n=16) - 13 JDM, 2 JPM and 1 JCDT-M	<u>Anti p140 + versus anti-p155/140-</u> - more muscle contractures, atrophy and a worse functional status (p value NR)
Tansley (2012)	<i>Controlled study</i> 172 JIIMs 1331 AIIMs	JIIMs: 11.6% (n=20) - all DM AIIMs: 0.8% (n=10)	<u>JIIMs: anti-p140+ versus anti-p140-</u> - significantly increased frequency of calcinosis, (p<0.05) <u>AIIMs: 3 had cancer (p=0.05)</u>
Shah (2013)	<i>Uncontrolled study</i> 436 JIIMs	IM: 19.7% (n=86) - 76 JDM, 3 JPM, 7 JCDT-M	NR

JIIMs: idiopathic inflammatory myopathies; A: adults; J: juvenile; JDM: juvenile dermatomyositis; JPM: juvenile polymyositis; JCDT-M: juvenile connective tissue disease associated myositis; CDT: connective tissue disease; NR: not reported.

TABLE III. SUMMARY OF THE STUDIES CARRIED ON THE ANTI-CADM 140 IN JIIMS

Author, year	Study/Population studied	Antibody frequency in JIIMs	Clinical associations
Kobayashi (2011)	<i>Uncontrolled study</i> 13 Japanese JDM	JIIMs: 39% (n= 5)	- 5 of the 6 patients with ILD -> anti-CADM 140+; - All of the 7 patients without ILD -> anti-CADM 140-; (p value NR)
Sato (2012)	<i>Uncontrolled study</i> 35 Japanese JDM - 26 classical JDM, 9 J CADM	JIIMs: 31% (n=11) - 6 classical JDM - 5 J CADM	- <u>Anti-CADM 140+ versus anti-CADM 140-:</u> significantly more RP-ILD; (p=0.05)
Betteridge (2012)	<i>Controlled study</i> 172 caucasian JDM + 1331 AIIMs 259 healthy controls and others CDT	JDM:7% (n=12) AIIMs: 1.9% (n=25) Controls: 0 patients	- <u>JIIMs: anti-CADM 140 +</u> - 0 had ILD - anti-CADM 140+ versus anti-CADM 140-: significantly more ulceration (skin and mouth); p<0.05) - <u>ADM: association with ILD (p<0.05)</u>

JIIMs: idiopathic inflammatory myopathies; DM: dermatomyositis; CADM: amyopathic dermatomyositis; A: adults; J: juvenile; ILD: interstitial lung disease; RP-ILD: rapidly progressive interstitial lung disease; CDT: connective tissue disease

TABLE IV. SUMMARY OF THE STUDIES CARRIED ON THE ANTI-P140 IN JIIMS

Author, year	Study/Population studied	Antibody frequency in JIIMs	Clinical associations
Tarricone (2012)	<i>Controlled study</i> 130 IIMs: - 12 JDM + 118 AIIMs 83 healthy controls and others CDT	- JIIMs: 0 - AIIMs: 4.2% (n= 5) - all DM - Controls: 0	NR
Shah (2013)	<i>Uncontrolled study</i> 436 JIIMs: 354 JDM, 33 JPM, 49 JCTD-M	IIMs: - 0.3% JDM (n=1) - 0 PMJ, 0 JCTD-M	NR
Muro (2013)	<i>Uncontrolled study</i> 110 DM: - 13 JDM + 97 ADM	- JIIMs: 0 - AIIMs: 2.1% (n=2)	NR
Fugimoto (2013)	<i>Controlled study</i> 456 DM - 11 JDM + 445 ADM 727 PM and with others CDT	- JIIMs: 9% (n=1) - AIIMs: 1.4% (n=6) - Controls: 0	The JDM case presented skin rashes that preceded muscle involvement

IIMs: idiopathic inflammatory myopathies; A: adults; J: juvenile; DM: dermatomyositis; PM: polymyositis; CDT: connective tissue disease; NR: not reported.

TABLE V. NOVEL MYOSITIS-SPECIFIC AUTOANTIBODIES IN JIIMS: TARGET AUTOANTIGENS, AND CLINICAL ASSOCIATIONS

MSA	Antibody target	Frequency	Clinical Associations
Anti-p155/140	Transcriptional intermediary factor 1 gamma (TIF1- γ)	22-36%	Severe cutaneous disease Ulceration
Anti-p140	Nuclear matrix protein 2 (NXP2)	12-25%	Severe disease Calcinosis
Anti-CADM-140	Melanoma differentiation-associated gene 5 (MDA5)	7-46%	RP-ILD in Japanese studies Ulceration in Caucasian cohort
Anti-SAE	Small ubiquitin-like modifier activating enzyme (SAE)	0.3-9%	Not known
Anti 200/100	3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)	Not known	Not known

(or anti-melanoma differentiation-associated gene 5 antibodies- MDA5) were first described in 2005 by Sato and colleagues in Japanese adult patients with clinically amyopathic dermatomyositis (CADM) and were associated with rapidly progressive interstitial lung disease (RP-ILD)¹⁶. In adults with IIMs, its frequency varies according to the population studied: in Japanese DM was present in 19-35%, while Caucasians cohorts reported a lower frequency⁶.

The CADM-140 autoantigen has been identified as

MDA5 from a DNA expression library. This protein is one of the retinoic acid-inducible gene-1-like receptors and has a role in the recognition of viral RNAs as part of the innate immune system⁵.

Anti CADM-140 has also been identified in JIIMs. In 2011, Kobayashi *et al.* evaluated the presence of this autoantibody in 13 Japanese patients with JDM. It was positive in 5 of the 6 patients with JDM-associated interstitial lung disease (ILD), but not in the 7 patients without ILD (Table III)¹⁷. Sato *et al.* studied 35 Japanese

patients with JDM; the anti-CADM 140 was positive in 31% of them and a strong association between anti-CADM-140 and RP-ILD17 was found¹⁸. Betteridge *et al.* evaluated a large cohort of Caucasian patients that included 172 JDM; ILD was associated with anti-CADM only in the adult population, while in JDM these authors found a significant association with ulceration¹⁹.

The reason for the discrepancy of the results is not clear but a potential role of genetic or environmental factors has been suggested to explain this difference¹⁹.

ANTI-SAE

Anti-SAE autoantibodies have been first described in adults with DM¹⁸. The target antigen of these antibodies is the small ubiquitin-like modifier (SUMO) activating enzyme, composed by two subunits SAE1 and SAE2 of apparent molecular weight of 40 and 90 kDa, respectively. SUMO is a small protein, structurally similar to ubiquitin, involved in post-translational modification of numerous targets²⁰.

In adults this antibody appears to be specific for DM and can be present in 2-8% of patients. Anti-SAE positive patients had mainly skin and muscle manifestations, while the data concerning the systemic involvement are more controversial²⁰⁻²³.

In children, the anti-SAE was evaluated in 4 different studies enrolling an overall of 472 patients with JIIMs and only two patients were positive for this antibody^{12,20-23} (Table IV).

ANTI-200/100

The most recent MSA, the anti-200/100, acts directly against the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR). This autoantibody was associated with immune-mediated necrotizing myopathy in adults and, interestingly, the majority of them had a history of exposure to statins²⁴. Studies suggest that statins trigger an autoimmune response against HMGCR by upregulating expression of this autoantigen²⁵. Nevertheless, to the best of our knowledge has not yet been studied in JIIMs.

DISCUSSION AND CONCLUSIONS

The traditional MSAs (anti-Jo-1, anti-SRP, and anti-Mi-2) are identified in approximately 40% to 50% of adult myositis patients and in less than 10% of JIIM⁵. In recent years, novel myositis-specific antibodies and their

autoantigen targets have been identified.

The present review highlights the higher frequency of these novel autoantibodies in JIIM compared to the traditional ones, as well as their potential value in defining distinct clinical subsets and in predicting disease course (Table V).

One of the most intriguing aspects of this review relates to the sound difference in clinical associations of these autoantibodies depending on age and ethnicity. Unlike adults, in fact, the anti-p155/140, the most frequently detected MSA in JDM is not associated to an increased risk of malignancy. Vice versa, similar to adults with anti-p155/140, JDM patients showed significantly more cutaneous involvement including ulceration and oedema. Of note the development of skin ulceration has been described as poor prognostic factor in JDM, being associated to the involvement of internal organs²⁶.

Also the anti-p140, which is uncommon in adults with IIM, appears to identify children with more severe disease course. In patients with JDM, in fact, anti-p140 was significantly associated with persistent disease activity, a worse functional status, and with the development of calcinosis. Further studies with multivariate regression analysis considering all the other potential factors implied in calcinosis development are however required to better elucidate the role of these autoantibodies in the onset of this disabling complication of JDM.

Why antibodies against the same target autoantigens are responsible for different clinical associations in childhood and adulthood remains unclear. It is unknown if these differences are related to differences in the pathogenesis and underlying disease trigger, or are a reflection of differences in cellular processes and immune function in different age groups⁵. It remains also unclear if these antibodies may be mediated by ethnic background or environmental factors. Of note anti-CADM-140 autoantibodies, whose autoantigen, the MDA5, is involved in innate immune responses against viral infections, were found in almost 50% of JDM patients in 2 Japanese cohorts; moreover, the association with rapidly progressive interstitial pneumonia, a peculiar life-threatening complication in JDM, was so far described only in Asian JDM patients. Future studies of larger, more ethnically heterogeneous populations of pediatric patients with JIIM are necessary to corroborate this data and to further characterize the clinical features and immunogenetic associations⁹.

To summarize, according to current evidence, the

anti-p155/140, anti-p140 and the anti-CADM-140 seem to be useful serological markers in JIIMs and may prove useful to generate predictors of clinical phenotype or disease outcome. Inadequate treatment has been shown to be a crucial factor in predicting a chronic course and poor outcome. By providing prognostic information these autoantibodies could be useful to tailor treatment according to disease severity and overall optimize treatment strategy.

The current testing approach based on immunoblot and immunoprecipitation assays are analytically powerful, but technically complex and time-consuming, and it cannot be applied on a large scale in the routine diagnostic setting²⁷. The future development of assays that test for MSAs in routine clinical practice is crucial in order to validate the clinical utility of these autoantibodies. Recently, the development and validation of a line blot assay containing a number of these MSAs demonstrates important progresses in this field⁵. Line blot could be a suitable serological test in the diagnostic workup for myositis and may represent a reliable alternative to more time-consuming procedures. Additional work is currently in progress to increase the accuracy of this technique^{27,28}.

Further studies, on the characterization of the autoantibodies in JIIMs, with a special focus on the structure and function of their targets molecules may provide further insight into pathogenic mechanisms of these complex diseases that in turn will stimulate new therapeutic approaches.

CORRESPONDENCE TO

Daniela Filipa Marinho Peixoto
Serviço de Reumatologia, ULSAM - Hospital Conde de Bertiandos;
Largo Conde de Bertiandos
4990-041 - Ponte de Lima, Portugal
E-mail: danielapeixoto81@hotmail.com

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